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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/323,803	06/10/99	LIU	M 19188PCA

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HM12/1012

EXAMINER	
LEFFLER JR,G	
ART UNIT	**PAPER NUMBER**
1634	11

DATE MAILED: 10/12/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/393,803	LIU ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-22,25,35,39-42,44 and 45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *18 and 39-41* is/are allowed.

6)☐ Claim(s) *1-3,12-15,19-22,25,35,42,44 and 45* is/are rejected.

7)☐ Claim(s) *4-11, 16-17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of applicants' amendment, filed 7/19/01 as Paper No. 11, in which claims were cancelled (claims 23-24, 26-34, 36-38 and 43), in which claims were amended (claims 1, 18, 22, 35, 39, 41-42 and 44) and which new claim 45 was added. It is noted that, after canceling claim 24, applicants' response also proposes an amendment of claim 24. As the claim had already been cancelled, and given that the body of applicants' response (e.g. page 7, response to rejection under 35 U.S.C. 112, first paragraph), the proposed amendment of claim 24 has not been entered.

Any rejection of record in Paper No. 8 not addressed in this action has been withdrawn. New rejections are made in this action which were not necessitated by applicants' amendment of the claims. Therefore, this action is not final. Claims 1-22, 25, 35, 39-42, 44-45 are pending.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 14-15, 42, 44 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,866,553 in view of Almond et al ((WO93/11250, published 10 June 1993; see the entire document) or Almond et al (GB 2 262 099A; see the entire document). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons.

The instant claims are directed towards polynucleotides which, upon introduction into a mammalian cell in vivo, are non-replicating and direct co-expression of at least two gene products. The vector can comprise several cistrons wherein each cistron is individually under control of transcriptional regulatory sequences (e.g. promoters, terminators). Alternatively, one or more of the cistrons comprised within the polynucleotide can be under the control of shared transcriptional regulatory sequences (e.g. the use of IRES sequences). The polypeptides encoded by the cistrons include antigenic polypeptides from pathogenic organisms or polypeptides associated with tumor cells.

Claims 1-4 of the '553 patent are directed towards a polynucleotide vaccine wherein the polynucleotide of the invention encodes at least one human papillomavirus (HPV) gene from a number of different HPV strains. Specifically claimed embodiments of the invention are the vectors V1Jneo and V1Jns. One of ordinary skill in the art, in order to understand the full metes and bounds of the specifically claimed vectors, and methods of use thereof, would have been compelled to read the specification wherein the vectors of the invention are described as being preferably non-replicative in eukaryotic cells and wherein the construction of the specific vectors is described.

Almond et al (both) teach a polynucleotide construction (page 4, top) which induces the expression of at least two gene products. The construction has at least a first eukaryotic promoter followed by a first cistron and a second cistron under the control of the first promoter, wherein an IRES is inserted between the two construct ructions. The IRES or ribosome landing pad sequences of EMCV and poliovirus are disclosed (page 5, lines 15-23).

It would have been obvious to one of ordinary skill in the art to construct a polycistronic vector encoding multiple HPV polypeptides as claimed in the '553 patent because the claims are directed to vectors expressing more than one of the viral polypeptides and because Almond et al teach it is within the skill of the art to construct polycistronic vectors comprising IRES sequences such that multiple viral sequences are expressed from the same construct. One would have been motivated to do so in order to obtain the expected benefit of obtaining a plasmid vector capable of expressing multiple HPV polypeptides in a mammalian cell in vivo. Absent any evidence to the contrary, there would have been a reasonable expectation of success in constructing and utilizing a non-replicating and polycistronic vector for expression of multiple HPV polypeptides in a mammalian cell in vivo.

Claims 1-3, 14-15, 42, 44 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 8, 10-11, 13-14 of U.S. Patent No. 5,736,524 in view of Almond et al ((WO93/11250, published 10 June 1993; see the entire document) or Almond et al (GB 2 262 099A; see the entire document). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons.

The instant claims are directed towards polynucleotides which, upon introduction into a mammalian cell in vivo, are non-replicating and direct co-expression of at least two gene products. The vector can comprise several cistrons wherein each cistron is individually under control of transcriptional regulatory sequences (e.g. promoters, terminators). Alternatively, one or more of the cistrons comprised within the polynucleotide can be under the control of shared transcriptional regulatory sequences (e.g. the use of IRES sequences). The polypeptides encoded by the cistrons include antigenic polypeptides from pathogenic organisms or polypeptides associated with tumor cells.

The claims of the '524 patent are directed to DNA vaccines comprising a plasmid vector wherein the vector encodes an antigen obtained from M. tuberculosis. The plasmid can be polycistronic wherein the plasmid also encodes an immunomodulatory polypeptide (e.g. a member of the B7 family of T-cell stimulatory polypeptides). Specifically claimed plasmids include V1Jns-85A(C2), V1Jns-85A(C3) and V1Jns-tPA-85A. One of ordinary skill in the art, in order to understand the full metes and bounds of the specifically claimed vectors, and methods of use thereof, would have been compelled to read the specification wherein the vectors of the invention are described as being preferably non-replicative in eukaryotic cells and wherein the construction of the specific vectors is described.

Almond et al (both) teach a polynucleotide construction (page 4, top) which induces the expression of at least two gene products. The construction has at least a first eukaryotic promoter followed by a first cistron and a second cistron under the control of the first promoter, wherein an IRES is inserted between the two construct ructions. The IRES or ribosome landing pad sequences of EMCV and poliovirus are disclosed (page 5, lines 15-23).

It would have been obvious to one of ordinary skill in the art to construct a polycistronic vector encoding multiple M. tuberculosis polypeptides as claimed in the '524 patent because the claims are directed to vectors expressing more than one of the viral polypeptides and because Almond et al teach it is within the skill of the art to construct polycistronic vectors comprising IRES sequences such that multiple viral sequences are expressed from the same construct. One would have been motivated to do so in order to obtain the expected benefit of obtaining a plasmid vector capable of expressing multiple HPV polypeptides in a mammalian cell in vivo. Absent any evidence to the contrary, there would have been a reasonable expectation of success in constructing and utilizing a non-replicating and polycistronic vector for expression of multiple HPV polypeptides in a mammalian cell in vivo.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 14-15 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff et al (U.S. Patent No. 6,228,844; see the entire document) in view of Almond et al ((WO93/11250, published 10 June 1993; see the entire document) or Almond et al (GB 2 262 099A; see the entire document).

Wolff et al (the '844 patent) teach the use of non-replicating constructs (RNA or plasmid DNAs) wherein the polynucleotide construct is used to deliver a pharmaceutical polypeptide to the interior of a cardiac cell of a vertebrate in vivo. In at least some embodiments the polynucleotide construct comprises multiple coding sequences wherein one of the coding sequences encodes an immunosuppressive polypeptide (e.g. cyclosporin) (e.g. Abstract; column 5, lines 24-28; column 49, lines 21-40). The '844 patent teaches that all forms of DNA, whether replicating or non-replicating, which do not become integrated into the genome, and which are expressible, are within the methods contemplated by the invention (column 7, lines 44-48). Plasmid DNAs suitable for use in the invention which are non-replicating in eukaryotic cells are described (column 9, lines 18-20). Effective doses for DNA or mRNA of the invention are described (e.g. 0.05 ug/kg to about 50 mg/kg; see column 12, lines 5-16).

Wolff et al do not explicitly teach the construction of embodiments of their invention wherein multiple polypeptides are encoded by a polycistronic message.

Almond et al (both) teach a polynucleotide construction (page 4, top) which induces the expression of at least two gene products. The construction has at least a first eukaryotic

promoter followed by a first cistron and a second cistron under the control of the first promoter, wherein an IRES is inserted between the two constructuctions. The IRES or ribosome landing pad sequences of EMCV and poliovirus are disclosed (page 5, lines 15-23).

It would have been obvious to one of ordinary skill in the art at the time of applicants' invention to construct a polycistronic plasmid encoding a polypeptide for stimulating vascular growth and encoding an immunosuppressive agent because Wolff et al teach it is within the skill of the art to utilize a polycistronic polynucleotide (e.g. mRNA or plasmid DNA) which is non-replicative in a eukaryotic cell to express multiple coding sequences and because Almond et al teach that it is within the skill of the art to construct polynucleotides comprising polycistronic sequences by incorporation of an IRES sequence. One would have been motivated to do so in order to receive the expected benefit of utilizing a vector which can express both a vascular stimulatory polypeptide was well as an immunosuppressive agent, as suggested by Wolff et al. Based upon the combined teachings above, and absent any evidence to the contrary, there would have been a reasonable expectation of success in constructing a polycistronic polynucleotide for the in vivo expression of both a vascular stimulatory polypeptide and an immunosuppressive agent in a target mammal.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-13, 19-22, 25, 35, 42, 44-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is vague and indefinite in that it specifies a specific order for a series of three genes in the polynucleotide of claim 1 and then recites "...wherein each of the cistrons may also be presented in a different order." The inclusion of the cited phrase makes it unclear as to the order of cistrons which is permissible. It appears the intended limitation is that the polynucleotide comprises the three specific coding sequences and that the three cistrons can be in any order. It would be remedial to amend the claim language to more clearly indicate which combinations of the three cistrons are acceptable.

Claim 19 is vague and indefinite in that it recites a series of sources for obtaining an immunogenic epitope but does so with improper Markush group language. It would be remedial to amend the claim to either delete the word "or" prior to the term "env" or include proper Markush group language (e.g. epitope selected from the group consisting of....and...".

Claim 20 is vague and indefinite in that it uses improper Markush group language. It would be remedial to amend the claim language to something like "...wherein the env immunogenic epitope is selected from the group consisting of .....and...".

Claim 25 is vague and indefinite in that there is no clear and positive prior antecedent basis in claim 1, upon which claim 25 is dependent, for the term "the vertebrate".

Claim 35 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "frames" in part (f) of the claim.

Claim 42 is vague and indefinite in that the metes and bounds of the phrase "...antigens related to disease causing pathogens or tumors...". What exactly are the criteria for determining if a particular polypeptide is "related to" a particular pathogen or tumor? It would be remedial to amend the claim language to more definitively indicate the types of genes claimed as part of the compositions.

Claim 44 is vague and indefinite in that the metes and bounds of the term "clinically relevant" are unclear (parts 8-9). Similarly, the metes and bounds of the phrase "...using the gene from clinically relevant strains (part 9) are unclear. It would be remedial to amend the claim to simply state that the gp160 is obtained from a clinical HIV isolate. Part 12 of claim 44 is vague and indefinite in that the section appears to specify a series of possible gp160 variants encompassed by the section. It would be remedial to avoid language like "such as" and to incorporate specific Markush group language to delineate between the different species of gp160 variants recited in part 12. Part 13 is vague and indefinite in that it is unclear what exactly constitutes an "appropriate leader sequence". Part 14 is vague and indefinite in that the metes and bounds of the phrase "...similar to construct from #5 above, using the gene from clinically relevant strains..." are unclear. Parts 17-18 appear to specify that any sequence, including any di-nucleotide sequence, from the recited genes is encompassed by the claim sections. It appears, upon reading the specification, that applicants may intend that the sections recite something like "...a sequence encoding GM-CSF . Regarding part 20 of claim 44, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 45 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "The polynucleotide..". It would be remedial to amend the claim to be either dependent upon another claim to provide antecedent basis, or amend the claim to read "A polynucleotide...".

Conclusion

Claims 1-22, 25, 35, 39-42, 44-45.
Claims 1-3, 12-15, 19-22, 25, 35, 42, 44-45 are rejected.
Claims 18, 39-41 are allowed.
Claims 4-11, 16-17 are objected to as being dependent upon a rejected claim. If re-written as independent claims incorporating each of the limitations of the claim upon which they depend, these claims would be allowable.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. §1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Leffers , Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on Monday through Friday, from about 9:00 AM to about 5:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Rob Schwartzman, Ph.D., can be reached at (703) 308-7307.

Any inquiry of a general nature or relating to the status of this application, or relating to attachments to this office action, should be directed to the Patent Analyst Zeta Adams, whose telephone number is (703) 305-3291.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

ggl
October 10, 2001

DAVID GUZO
PRIMARY EXAMINER